



U.S. - Australia Biomedical Research Partnership Conference

Monday, 13 July 2015, Canberra Australia

*United States Embassy
University of Canberra
National Health and Medical Research Council
Australian Academy of Science
Australian Academy of Health Medical Sciences,
National Institutes of Health
Department of Industry and Science*

United States–Australia Biomedical Research Partnership

Table of Contents

ABSTRACTS

GENOMICS AND INFECTION RESEARCH
MOLECULAR AND CELLULAR RESEARCH
CLINICAL AND APPLIED RESEARCH
PUBLIC AND MENTAL HEALTH RESEARCH

BIOGRAPHIES

GENOMICS AND INFECTION RESEARCH

Genetics in the developing world

Simon Foote, Brendan McMorran, Gaetan Burgio
John Curtin School of Medical Research

Genetics is being used to target specific therapies to individuals who need this therapy. This will improve the treatment of disease and will enable less wastage of drugs and time in the initial phases of therapy. However this is an expensive approach and its use will be limited to the developed world. We are using genetics to try and benefit the developing world. We have developed a genetic screen to search for novel antimalarial drugs. These drugs will target the host and not the parasite. They should be resistant to changes in the parasite that render current therapies useless.

We are also examining renal disease in the Indigenous Australian population. We have performed a GWAS across 330 Indigenous Australians from a community with elevated renal disease. We have several regions of association that we have validated in a second cohort of 500 individuals. Genome sequence data has provided several candidate genes that are involved in renal development that are also mutated in this population.

Susceptibility Genes for Endometriosis

Grant W. Montgomery

Genetics and Computational Biology Department, QIMR Berghofer Medical Research Institute

Insight into the genetic architecture and specific genes underlying complex human diseases has been possible by combining advanced genomic technologies with existing sample collections. We recruited large twin samples and disease cohorts with colleagues in the US and have since identified genetic risk factors for a range of human diseases including nicotine dependence, melanoma, psychiatric disorders, and endometriosis. These projects have been supported with funding from the NHMRC, NIH and US philanthropic funds.

Results from genome-wide association studies demonstrate the genetic risk for complex diseases results from many genes of small effect. Consequently, international collaborations are increasingly important to advance our understanding of genetic risk and the biology of complex diseases. Endometriosis is a disease with lesions of endometrial-like tissue located in the peritoneal cavity and affects 6-10% of women during their reproductive years. It is a major cause of pain and infertility with very significant healthcare costs and loss of productivity for women suffering from the disease. The cause remains poorly understood. We have identified genomic regions associated with disease risk and begun to identify specific genes affected by genetic risk factors in each of the regions. We are working with the US Nurses' Health Study, the US Women's Genome Health Study and other international groups to conduct the next major studies to understand this enigmatic and costly disease.

Acknowledgements: I thank the many colleagues who have contributed to these studies and funding from the Australian National Health and Medical Research Council, The United States National Institutes of Health, and the Melanoma Research Alliance.

Whole genome sequencing and systems approach to inflammatory and immunological diseases: successful US-Australia partnerships in “big science”

Christopher C Goodnow
Member, US National Academy of Science
Deputy Director, The Garvan Institute of Medical Research
Adjunct Professor, The Australian National University
Conjoint Professor, University of New South Wales

Whole genome sequencing has recently advanced to the point where it is now possible to identify most of the DNA sequence differences in a person's genetic blueprint, for little more than the cost of a magnetic resonance image.

Since each person has thousands of DNA differences, the big challenge now is how to interpret those differences to unlock major advances in the precision and efficiency of medical diagnosis, treatment, and prevention.

Interpreting the functional significance of human DNA differences will require global collaborative efforts, linking large scale whole genome sequencing and clinical observations with computation, databases, epidemiology, and direct experimental testing.

Here I will summarize discoveries, lessons and opportunities from a large US-Australia collaborative effort to define how DNA sequence variants affect the body's immune and inflammatory systems. This program has been funded by the US NIH National Institute of Allergy and Infectious Disease (NIAID) and by the Australian Commonwealth Government's National Collaborative Research Infrastructure Scheme (NCRIS). It links the Australian National University and the Garvan Institute for Medical Research in Australia with the Scripps Research Institute, University of Texas Southwestern Medical Centre, Stanford University and Seattle Biomedical Institute.

This program has created a publicly available international research resource of unparalleled scale for experimentally testing the connections between DNA sequence variants and any aspect of physiology or pathology. The resource has in turn catalyzed a large, ongoing, Australia-US commercial partnership with Genentech.

This example provides a model for successful “big science” biomedical partnerships leveraging complementary skills and resources in Australia and the United States of America.

Molecular genetics of migraine: diagnostic and therapeutic implications

Lyn Griffiths

Genomics Research Centre, Institute of Health and Biomedical Innovation, Queensland University of Technology

Migraine is a severe neurological disorder that affects a significant proportion of the population. Prevalence estimates for the disorder vary between 12 and 25% depending on the population studied. The disorder has a significant genetic component showing high levels of familial aggregation and a number of genes involved in rare and severe sub-types of migraine have been identified. However, the number and identity of all the genes involved in the more common types of migraine have yet to be defined. Genetic linkage and GWAS studies have implicated a number of genomic regions and several susceptibility variants in the disorder. Neurotransmitter pathways have been the main focus of studies investigating the molecular mechanisms of the disorder. However vascular and hormonal disturbances also occur in migraineurs, as highlighted by alterations in cerebral blood flow and hormonal triggers of migraine. This presentation will focus on our migraine gene studies and the translational outcomes of this research, including the development and use of a NGS diagnostic to identify severe migraine and related cerebrovascular, ataxia and epilepsy disorders, as well as the results of clinical trials investigating a gene targeted nutraceutical based therapeutic for migraine.

How NIH funding helped create an Australian resource for the -omics era

Nick Martin

QIMR Berghofer Medical Research Institute

In the 1980s there was growing interest in the role of genetic factors in behavior, psychiatric disease, and the addictions in particular. Having started the Australian Twin Register in 1978, and in our first survey in 1980 obtained extensive data on drinking and smoking habits on nearly 4000 adult twins, we were well-positioned to obtain NIH funding to expand this work in a number of directions over the next 20 years, obtaining detailed longitudinal data on use and abuse of alcohol, nicotine, cannabis, opioids, other drugs, and also gambling. We also queried concomitant psychiatric dimensions including depression, anxiety, conduct disorder, and risk factors including traumatic life events (including childhood sexual abuse) and protective factors including social support from spouses, family members and friends. At first we used mailed questionnaires, but psychiatrists didn't give these data much credence so we switched to telephone interviews which were much more expensive but allowed more nuanced phenotyping. More recently we have moved to online surveys. In total we obtained detailed phenotypic data on >20,000 twins and family members. Main conclusions were that use of, and addiction to, all these substances were strongly genetically influenced, up to 60%, equally in men and women, and that there was some genetic overlap between substances, but also genetic factors specific to substances.

Being good scientific reductionists we were not content to stop there but wanted to know what the actual genes were behind these heritabilities. Beginning 1993, and once again with NIH funding, we started massive "bleedathons" of our twins in all capital cities. This created a huge task for our wet lab, ably directed by Grant Montgomery, but eventually we ended up with DNA, serum, plasma and red cell fractions stored for >30,000 individuals and a biobank of some half million specimens. The initial hope in the 90s and until ~2005, is that we could use genetic linkage analysis to find genes predisposing to complex traits but, after much investment in microsatellite genotyping, it became clear that the effects we were looking for were much smaller than could be detected by linkage. Just at that time, in 2005, the first "SNP chips" became available, enabling genomewide association scans (GWAS) and these had immediate success in finding genes predisposing to some diseases, most notably macular degeneration, with quite small numbers of cases and controls. However, it soon became apparent that for most diseases and traits much larger sample sizes were needed to find the genes.

And so began perhaps the most remarkable sociologic change in the conduct of science, as big-name labs realized they could not achieve glory by themselves, but had to collaborate with others, including their erstwhile rivals, and had to spend a considerable amount of their time on international teleconferences at all hours of the day and night with their GWAS consortium collaborators. But the outcome has been remarkable with more progress on the genetic of complex disease in the past five years than in the entire previous history of the subject; we now have thousands of significant "hits" for hundreds of diseases and important biomedical traits, providing myriad leads for development of new therapeutics. Being so well prepared with detailed phenotyping in many domains and DNA available on >20,000 samples, our group has been well positioned to take part in most of the big GWAS consortia, and we have been on >200 important GWAS papers since 2007, at one time contributing around 5% of total global GWAS output. Our resource is of continuing value with methylomics, transcriptomics, metabolomics data being collected and soon we anticipate large scale whole genome sequencing.

All this was made possible by the generous and far-seeing funding policies of NIH over almost a quarter century which has fuelled many lively collaborations with US groups, and arguably, an incredibly effective soft projection of American power and influence. With the steep decline in US funding this has largely come to a stop, to the detriment of both sides. It would be good to revive it in some guise.

New inhibitors of HIV-1 reverse transcriptase

Jennifer La^{1,2}, Catherine F Latham¹, Adam Johnson¹, David Tyssen¹, Stephen Headey², Nicholas Barlow², Martin Scanlon^{2,3}, Jamie S. Simpson², Philip Thomson², Joseph Bauman⁴, Eddy Arnold⁴, Kelly Huber⁵, Nicolas Sluis-Cremer⁵, David Chalmers², Gilda Tachedjian^{1,6,7,8}

¹Centre for Biomedical Research, Burnet Institute, Melbourne, VIC, Australia, ²Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, VIC, Australia, ³ARC Centre of Excellence for Coherent X-ray Science, Australia, ⁴Centre for Advanced Biotechnology and Medicine, Department of Chemistry and Chemical Biology, Rutgers University, Piscataway, NJ, USA, ⁵Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA, ⁶Department of Microbiology, Monash University, Clayton, VIC, Australia, ⁷Department of Infectious Diseases, Monash University, Melbourne, VIC, Australia, ⁸Department of Microbiology and Immunology, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Parkville, VIC, Australia.

With an estimated 35 million HIV-infected individuals worldwide in 2013, the HIV/AIDS pandemic continues to pose a serious global health threat. Current treatment involves combination antiretroviral therapy (cART), a regimen comprising three or more drugs from at least two drug classes. HIV drug resistance, dosing schedules that reduce patient compliance, and toxicity can limit the effectiveness of cART. Additionally, strategies for HIV pre-exposure prophylaxis (PrEP) that have been approved (i.e., Truvada), or are in development, use existing HIV drugs that could lead to the generation and transmission of drug-resistant strains in a real-life setting and compromise first-line drug regimens in resource-constrained countries. Consequently, there is a need for new classes of antiretroviral drugs with novel mechanisms of action to combat drug-resistant strains for the treatment and prevention of HIV. To address this need we have assembled a multi-national and multi-disciplinary team that is employing fragment-based drug design to discover novel active site and/or allosteric inhibitors of HIV reverse transcriptase (RT). Using saturation transfer difference (STD) NMR and in vitro activity assays, we have identified fragment-sized inhibitors of HIV-1 RT with distinct chemical scaffolds and mechanisms compared to nonnucleoside RT inhibitors (NNRTIs) and nucleoside/nucleotide RT inhibitors (NRTIs) used in the clinic. Three compounds were found to inhibit RNA- and DNA-dependent DNA polymerase activity of HIV-1 RT in the micromolar range while retaining potency against RT variants carrying major NNRTI resistance mutations. Steady-state kinetic analyses using expertise from our collaborator Nicolas Sluis-Cremer (University of Pittsburgh, USA) demonstrate that one of these fragments is a competitive inhibitor of HIV-1 RT with respect to deoxyribonucleoside triphosphate (dNTP) substrate, whereas a second compound is a competitive inhibitor of RT polymerase activity with respect to the DNA template/primer (T/P), and consequently also inhibits RNase H activity. The dNTP competing RT inhibitor retains activity against the NRTI-resistant mutants K65R and M184V, demonstrating a drug resistance profile distinct from the nucleotide competing RT inhibitors indolopyridone-1 (INDOPY-1) and 4-dimethylamino- 6-vinylpyrimidine-1 (DAVP-1). In antiviral assays, the T/P competing compound inhibits HIV-1 replication at a step consistent with an RT inhibitor. Structure activity relationship studies of the three fragments have led to the discovery of molecules with improved potency against HIV-1 RT. One of these molecules has been co-crystalized with HIV-1 RT by the Arnold laboratory (Rutgers University, USA) and binds to a novel pocket with this finding currently being validated by mutagenesis studies. These fragment inhibitors represent previously unidentified scaffolds for elaboration into novel drugs for HIV-1 prevention or treatment.

Targeting the cell stress response of *plasmodium falciparum* to overcome artemisinin resistance

Leann Tilley¹, Stanley C. Xie¹, Con Dogovski¹, Jess Bridgford¹, Gaetan Burgio², Simon Foote², David A. Fidock³, Sachel Mok⁴, Zbynek Bozdech⁴, Kesinee Chotivanich⁵, Arjen M. Dondorp⁵, Hao Li⁶, Matt Bogyo⁶, Nick Klonis¹

¹Department of Biochemistry & Molecular Biology, Bio21 Institute, The University of Melbourne, Melbourne, VIC, Australia, ²John Curtin School of Medical Research, the Australian National University, Canberra ACT, Australia, ³Department of Microbiology and Immunology, Columbia University Medical Center, New York, USA, ⁴School of Biological Sciences, Nanyang Technological University, 637551 Singapore, ⁵Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, ⁶Stanford University School of Medicine, Stanford, CA USA

Malaria remains a scourge of humanity, affecting hundreds of millions of people and causing 600,000 deaths each year. At present, artemisinin derivatives (ARTs) remain the last line of defence against this debilitating disease. Thus reports that resistance of ARTs has emerged along the Thailand-Cambodian border¹, and that its prevalence is increasing² are particularly alarming. The WHO has warned: "There is a finite window of opportunity to contain artemisinin resistance. If the current foci of artemisinin-resistant parasites are not contained or eliminated, the costs, both human and financial, could be great".

Recent work has shed light on the underlying genetics associated with resistance, culminating in the identification of a genetic marker (Kelch protein propeller domain; K-13) that appears to be associated with the resistance phenotype *in vitro* and *in vivo*³. However the underlying mechanism remains unclear.

We undertook a detailed kinetic analysis⁴ of the drug responses of K13 wildtype and mutant isolates of *Plasmodium falciparum* sourced from a region in Cambodia (Pailin). We demonstrated that ART treatment induces growth retardation and an accumulation of ubiquitinated proteins, indicative of a cellular stress response that engages the ubiquitin/ proteasome system⁵. We showed that resistant parasites exhibit lower levels of ubiquitinated proteins and delayed on-set of cell death, indicating an enhanced cell stress response. We found that the stress response can be targeted by inhibiting the proteasome. Accordingly, clinically-used proteasome inhibitors strongly synergize ART activity against both sensitive and resistant parasites, including isogenic lines expressing mutant or wildtype K13. Synergy is also observed against *P. berghei* *in vivo*. Our work provides a rationale for improving the detection of ART resistance in the field and for treatment strategies that can be employed in areas with ART resistance.

Interactions with US colleagues

My lab is working as part of a global effort to understand the action of and resistance to artemisinin, with a view to designing better antimalarial drugs. We are working with Matt Bogyo, Stanford University, a synthetic chemistry who is generating plasmodium-specific proteasome inhibitors; with David Fidock, Columbia University, who is generating K13 mutant transfectants; and Larry Dick, Director of Research at Takeda Oncology in Cambridge, MA. As part of Millennium Pharmaceuticals, Inc (acquired by Takeda in 2008), Dr Dick developed the orally-available proteasome inhibitor, ixazomib, and the ubiquitin activating enzyme inhibitor, MLN72.

Relating proteomes, epitope abundance and immune responses to virus infection

David C Tscharke^{1,2}, Nathan P Croft³, Stewart A Smith², Yik Chun Wong², Inge EA Flesch², Anthony W Purcell³

¹*John Curtin School of Medical Research and* ²*Research School of Biology, The Australian National University;* ³*Biochemistry and Molecular Biology, University of Monash*

The human immune system has several mechanisms by which cells with anti-viral function can recognise and respond to infection. CD8⁺ T cells are a key immune cell type in defence against viruses because they can recognise and kill infected cells. This recognition is based on the binding of T cell receptors on the CD8⁺ T cell, to antigens in the form of peptides complexed with MHC I proteins displayed on infected cells. MHC I proteins are expressed on the surface of most cells and the peptides displayed reflect the proteome in each cell. However, many aspects of the presentation of viral peptides on MHC I for recognition by CD8⁺ T cells remain untested empirically having been extrapolated from simple model antigen systems or drawn from theory. To address these gaps, we have been using advanced mass spectrometry methods to analyze the presentation of many native vaccinia virus antigens by MHC I on mouse cells and correlating this information with the CD8⁺ T cell response during infection. With this information we show: 1) Presentation of viral peptides on MHC I during virus infection is complex and dynamic. 2) There are substantial cell type differences in the presentation of many epitopes, with some peptides differing in presentation level by more than 10-fold between DC-like and epithelial-like cell lines. 3) Most (~90%) of viral epitopes are generated from their source protein co-incident with expression. 4) The infected cell surface is poorly reflected in the anti-viral CD8⁺ T cell repertoire, with many highly abundant peptide-MHC complexes eliciting only weak or non-existent responses. 5) In collaboration with the US-based Immune Epitope Database (IEDB) we are using our experimentally derived data to test the performance and aid development of tools that can be used to predict MHC I-presented peptides. Our work in this area demonstrates that there are many surprises waiting in viral immunopeptidomes and there is an urgent need for more data if we are to manipulate this aspect of immunity to develop better vaccines.

Leukocyte biology in development and disease

Graham J. Lieschke

Australian Regenerative Medicine Institute, Monash University,

Leukocytes (white blood cells), most particularly neutrophils and macrophages, are the frontline of host defence against microbial infection. Patients with depleted leukocyte numbers, or with defects of leukocyte function, are prone to recurrent and sometimes life-threatening infection. When white blood cell growth is dysregulated, diseases like leukaemia and myelodysplasia result.

From studies using genetic approaches in zebrafish models, we have discovered new pathways regulating leukocyte development, and by exploiting the optical transparency of zebrafish embryos, we have observed novel leukocyte behaviours as they are deployed during infection.

A forward genetic screen for zebrafish mutants with reduced leukocyte numbers identified diverse genes important for leukocyte development. These include: *alk8* (a receptor for BMP signalling), a group of genes involved in transcriptional regulation (*med12*, *pol2b*, *zbtb11*), a splicing factor (*prpf8*) and unmasked the role of the microRNA *miR-451* in fine-tuning blood cell development. These studies enhance the understanding of the pathogenesis of congenital and acquired blood diseases and point to treatment targets.

Using zebrafish infection models and new transgenic zebrafish lines, we have studied leukocyte behaviour by *in vivo* 4-D imaging, to better understand the cell biology of their protective function. We have discovered new mechanisms regulating the attraction and departure of leukocytes at sites of infection and inflammation. In fungal infection models, shuttling of individual microorganisms between neutrophils and macrophages has unexpectedly been detected. We are observing with unprecedented clarity the recently-recognised behaviour of neutrophils to form extracellular traps that ensnare microorganisms. These studies provide an anatomical basis for understanding how these cellular behaviours are molecularly regulated, for explaining their contribution to host defence, and for looking for ways to therapeutically take advantage of them.

This work was directly funded by NIH through RO1-HL079545 "Congenital myeloid failure syndromes in mutant zebrafish" (2004-9) and multiple NHMRC grants. Productive collaborations have involved US scientists at Harvard Medical School (Boston, MA), University of California (San Diego, CA), University of Chicago (IL), University of Washington (Seattle, WA), and Cleveland Clinic (OH).

U.S.-Australia malaria vaccine initiative

Michael Foley¹, Sheetij Dutta², James G. Beeson³, and Robin F. Anders¹.

¹*Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Australia.* ²*Department of Epitope Mapping, Walter Reed Army Institute of Research, Silver Spring, USA.* ³*Centre for Biomedical Research, Burnet Institute, Melbourne, Australia.*

Malaria affects millions around the world and a vaccine that either prevents malaria or lessens its disease burden will have a significant global impact. Apical membrane antigen-1 (AMA1) is considered one of the most promising asexual blood-stage antigens for inclusion in a vaccine against *Plasmodium falciparum*, the cause of the most serious form of human malaria. Preclinical studies in rodent and simian models of the human disease have provided much evidence that AMA1 can induce immune responses that protect against malaria challenge and that antibodies that block merozoite invasion are an important mediator of the protective anti-AMA1 immune response. Vaccination with a single AMA1 strain showed protection against malaria among vaccinated children living in Mali. However, this protection was only observed against one strain of the parasite that resembled the vaccine strain. Lack of protection against non-vaccine strains, makes it difficult to produce a globally effective AMA1 vaccine, given that hundreds if not thousands of strain are circulating in the field.

In a joint US-Australia collaborative program we have used crystal structure data and monoclonal antibodies, as well as a novel approach using transgenic *P. falciparum* with defined mutations in AMA1 sequences to identify regions of AMA1 molecule that induce strain-transcending antibodies. It was found that AMA1 with specific mutations in this highly polymorphic region can dampen the antibody response to dominant strain-specific epitopes and could induce a more broadly cross-reactive antibody response. We have also shown that a Quadrivalent vaccine (Quadvax) induces antibodies that specifically focus host immunity towards these broadly cross-reactive regions of AMA1. We describe the location of these broadly inhibitory regions (epitopes) and a method to induce antibodies to these regions using the Quadvax. This information can now be used to develop a second-generation vaccine that focuses the host immunity towards these susceptible regions that are common among all strains.

MOLECULAR AND CELLULAR RESEARCH

The transformational impact of cancer immunotherapy on contemporary clinical practice.

Jonathan Cebon

Olivia Newton-John Cancer Research Institute

The focus of our translational research program over 20 years has been melanoma and the immune therapy of cancer. We have evaluated strategies aimed at enhancing anticancer immunity. These approaches have included antibodies directed against cancer, cytokines to enhance immune responses such as Granulocyte-Macrophage Colony Stimulating factor (GM-CSF), Interleukin (IL)-12 and Flt3Ligand and cancer vaccines based on peptides and proteins derived from tumor antigens. The epigenetically-regulated Cancer-Testis (CT) antigen NY-ESO-1, has been a particular focus. These studies have provided considerable insights into the interface between human immunity and cancer.

The most impressive progress in the field, however, has emerged in recent years using agents that target the molecular regulators of cellular immunity; antagonists of Cytotoxic T-Lymphocyte Antigen 4 (CTLA4), Programmed Death (PD)-1 and its ligand (PD-L1). Monoclonal antibodies that block these immune checkpoints are inducing regressions in a majority of patients with advanced metastatic melanoma, particularly when administered in combination. Additionally, emerging clinical data is now showing impressive clinical activity in many other cancer types including cancers of lung, bladder, kidney, head & neck, stomach and lymphoma.

Ongoing clinical trials are now evaluating combination approaches that bring together insights developed by studying antigen-specific immune responses with those that have enabled us to interfere with the regulatory processes that suppress anti-cancer immunity. These clinical trials highlight the value of iterative translational research that links laboratory with clinic.

Role of HDAC3 in regulating metabolism and cancer in the gastrointestinal tract.

John M. Mariadason

Olivia Newton John Cancer Research Institute

Histone deacetylases (HDACs) are a family of epigenetic regulatory proteins comprising 18 members. A key function of these enzymes is catalysis of the deacetylation of lysine residues in histone proteins, which causes the inactivation of gene expression. Conversely, inhibitors of these enzymes (HDAC inhibitors or HDACi) enhance gene expression and induce a range of cellular effects, most notably the induction of apoptosis in cancer cells. As a result HDACi have been extensively investigated as potential anti-cancer agents, and 3 HDACi are now clinically used in the treatment of haematological cancers. The goal of our laboratory is to investigate whether HDACi may also have use in the treatment of colon cancer, and to elucidate the biological function of individual HDACs in the gastrointestinal tract. Our work to-date has identified a subset of colon cancer cell lines that are highly responsive to HDACi, and we have established the mechanistic basis for this sensitivity. Among individual HDACs, we have focused primarily on defining the biological function of HDAC3. We have demonstrated that HDAC3 expression is elevated in colon cancers, that it is required for the proliferation of colon cancer cells, and that this effect is mediated by inactivating expression of the growth inhibitory gene, p21. Recently, using conditional knockout mice, we have also identified a novel role for HDAC3 in regulating lipid catabolism in the intestinal epithelium, and we are currently exploring whether inhibition of HDAC3 in this tissue may represent a novel strategy for reducing weight gain. These studies have been made possible by 2 NIH RO1 grants, NHMRC project grants and Fellowships and ongoing collaborations between scientists in Australia and the United States.

A humble brain in a box: how the neurosensory apparatus in decayed teeth reveals remarkable insight into the central nervous system of man

Neil Hunter

Institute of Dental Research; University of Sydney

Introduction: The peripheral aspect of tooth pulp has a central nervous system-like structure comprising sensory cells (odontoblasts) connected to glial processes that also link to a deeper blood-brain barrier microvasculature.

Response to caries: The complex polymicrobial infection typical of chronic progressive caries triggers a major response in this neurosensory network. A radically altered calcified matrix protects against microbial invasion. To support increased metabolic activity by odontoblasts that deposit altered calcified matrix glial cells proliferate and align vertically to support development of new vascular loops that ascend towards the odontoblasts while maintaining barrier integrity.

Neurogenesis: The vascular response enables a second, linked response. Glial cells seek out and liberate selected pericytes from the outer layer of the vascular loops. These cells proliferate and ascend the glial processes to differentiate as glial cells or nerve cells according to the microenvironment.

Mechanism: The gene encoding Notch1 plays a central role in laying down orderly tissue patterns. Our findings indicate that Notch1 also exerts master control over the linked vascular-neurogenic response. Further investigation revealed that a small regulatory nucleic acid molecule we termed Voyager, had powerful effect in driving the generation of nervous system elements from recruited pericytes. Voyager achieves this action by regulating a large number of genes implicated in nervous system development. Bioinformatic and experimental analysis confirmed that the potential of Voyager is only achieved in man.

Conclusion: Unexpectedly the infection of caries was shown to impact on a neurosensory structure similar in overall features to the retina of the eye. The adaptive response of the neurosensory components provided access to the mechanism of response revealing a new aspect of neural differentiation in man.

Small molecules to inhibit BAX/BAK-mediated apoptosis

Professor David Huang
Walter and Eliza Hall Institute of Medical Research

Growth factor regulation of lens cell behaviour in health and disease

McAvoy JW¹, Sugiyama Y¹, Dawes LJ¹, Lovicu FJ^{1,2}

¹ Save Sight Institute, University of Sydney; ² Discipline of Anatomy and Histology, Bosch Institute, University of Sydney,

Cataract is the most common cause of blindness in the world today. Whilst surgery is generally very effective, complications such as the aberrant regrowth of lens cells that lead to secondary cataract formation are all too common. Our aim is to understand how to supplant aberrant growth with normal cell growth and differentiation so that ultimately we can devise strategies to regenerate lens structure/function. Achieving this depends on understanding the factors/conditions that drive formation of the lens in the first place; i.e. during embryonic development.

Lens develops its distinctive spheroidal structure because cells in the posterior half of the lens vesicle elongate and differentiate into primary fibres, whereas cells in the anterior half differentiate into small cuboidal epithelial cells that cover the anterior poles of the highly elongated fibres. The lens maintains its spheroidal shape as it grows by spatially coordinated epithelial to fibre differentiation. There is now compelling evidence from our lens epithelial explant studies that FGF growth factor signalling initiates and promotes the epithelial to fibre differentiation process. However, understanding lens morphogenesis depends, not only on knowing how to trigger fibre differentiation, but also how to recapitulate the processes that result in differentiation and assembly of both epithelial and fibre cells, into the highly ordered and polarised three-dimensional structure that transmits and focuses light onto the retina.

Our studies indicate that as fibres undergo early stages of elongation their alignment and orientation depends on Wnt-Frizzled/Planar Cell Polarity signalling. Explant studies show that FGF-induces upregulation of Wnt-Fz signalling components and this is accompanied by translocation of Fz and the centrosome/primary cilium to the leading edge (apical tip) of similarly polarised groups of elongating fibre cells that orient towards islands of epithelial cells. Recent evidence indicates that this polarised/oriented behaviour is in response to epithelial-derived Wnt5A. In addition, we reveal a reciprocal interaction where elongated fibres promote Jagged/Notch signalling that is required for maintaining the epithelial phenotype. This provides key insights into an FGF-activated mechanism intrinsic to the lens that involves interactions between the Wnt-Fz and Jagged/Notch signalling pathways.

This reciprocal interaction appears to be critical for assembly/maintenance of the highly ordered three-dimensional architecture that is central to lens function. This provides insights into how to regenerate functional lenses from epithelial layers and so far we have developed a rat model for lens regeneration in vitro. This progress has only been possible because of grants from the National Institutes of Health (NIH) over the last 33 years. A priority area initially identified by the National Eye Institute as part of its cataract program was to '*...develop new techniques to study the embryology and morphology of the lens...*'. Our work with lens epithelial explants filled that niche and through this partnership has opened up new areas of research that are yielding new insights into lens developmental biology. Through collaboration with US colleagues, I have no doubt that we will be able to devise strategies for lens regeneration after cataract surgery in the not too distant future.

Using the breast epithelial hierarchy to decipher breast cancer

Jane Visvader and Geoffrey Lindeman (in collaboration with Genentech, AbbVie and Amgen USA)
The Walter and Eliza Hall Institute of Medical Research
The University of Melbourne
The Royal Melbourne Hospital

Breast cancer is a highly heterogeneous disease at both the molecular and pathological levels. To understand this heterogeneity and 'cells of origin' of breast cancer, it is important to dissect the normal mammary epithelial hierarchy. Lineage tracing is a key strategy for assessing the stem cell hierarchy as it allows stem and progenitor cell fate to be studied *in situ* in the context of development, tissue maintenance and disease. We have combined lineage tracing with a novel three-dimensional imaging strategy to explore the relative contributions of stem and progenitor cells to post-natal mammary gland development and tissue homeostasis. Cell lineage tracing studies also provide the current gold standard for identifying 'cells of origin' in cancer. Towards this end, we are utilizing newly generated transgenic strains harbouring lineage-specific gene regulatory regions to direct the expression of specific mammary oncogenic lesions to discrete epithelial cell types.

In terms of human breast cancer, the interrogation of molecular profiles has provided insight into potential 'cells of origin' in pre-neoplastic tissue for basal-like cancers arising in *BRCA1* mutation carriers. The identification of deregulated genes/pathways in these crucial target cell populations may enable earlier detection of malignancies and lead to preventive therapies for individuals at high risk of developing breast cancer (in collaboration with Amgen).

To test new therapies for breast cancer, we have generated an extensive bank of patient-derived xenografts (PDXs) from primary breast cancers. These include ER-positive, HER2-positive and triple negative tumours, which lack oestrogen receptor (ER), progesterone receptor (PR), and HER2/ERBB2 expression. These were derived through orthotopic transplantation of primary breast tumour tissue into the mammary fat pads of immunocompromised NOD-SCID-IL2R γ ^{-/-} mice. Such models offer significant advantages over cell line-based xenografts, as they recapitulate features of the primary tumour. We have evaluated BCL-2 as a potential therapeutic target in ER-positive breast cancer, given that this pro-survival protein is frequently overexpressed in this type of breast cancer (in collaboration with Genentech and AbbVie). The BH3 mimetic ABT-737 markedly improved tumour response to the anti-oestrogen tamoxifen. Despite abundant BCL-XL expression, similar efficacy was observed with the BCL-2 selective inhibitor ABT-199, revealing that BCL-2 is a crucial target. These findings provide a rationale for the clinical evaluation of BH3 mimetics in therapy for breast cancer and validate the use of patient-derived xenografts as preclinical models for exploring new 'druggable' targets.

Non-alcoholic steatohepatitis

Geoffrey Farrell
Australian National University

More than 30% of the Australian and North American population have a fatty liver (NAFLD) related to overweight/obesity and its complications, such as type 2 diabetes and metabolic syndrome. Nonalcoholic steatohepatitis (NASH) is the inflammatory, pro-fibrotic form of NAFLD that can lead to cirrhosis. Despite decades of research, there is no drug treatment for NASH, largely because the molecular pathogenesis has not yet been characterised. Our research at ANU, in collaboration with groups at UW Seattle and UC San Diego, uses a mouse model, *Alms1* mutant or *foz/foz* mice that have a hypothalamic eating disorder. This drives them to consume enormous quantities of food, resulting in obesity/inactivity, diabetes, high blood pressure, hypercholesterolemia and NASH. We have used this model to test the concept that NASH, like type 2 diabetes, is a form of lipotoxicity – tissue injury caused directly by toxic lipid species. Here we will briefly review the evidence that the toxic lipid species causing NASH is free cholesterol, and show how in primary hepatocytes cholesterol injures liver cells by a JNK1-mediated mitochondrial pathway. Our novel observation that *Jnk1*^{-/-} hepatocytes are refractory to and potent, specific JNK inhibitors protect cells against free cholesterol lipotoxicity opens a new pharmacological approach to NASH therapy.

Innate immunity is the pathway to inflammatory recruitment in NASH. We will describe evidence that TLR4, activated by HMGB1 and other DAMPs, is an essential trigger for NASH. Most recently, in collaboration with Seattle colleagues (George Ioannou et al) we observed that cholesterol crystals form in *foz/foz* mouse livers with NASH (as in the human condition), and this is associated with activation of the NLRP3 inflammasome. This can be modelled in primary cultures of Kupffer cells, and provides an *in vitro* system to assess novel NLRP3 inhibitors under development by colleagues at the Institute for Molecular Bioscience at the University of Queensland (Avril Robertson and Matthew Cooper). Preliminary drug intervention studies in *foz/foz* mice indicate that such compounds may be highly effective therapy for NASH, completely reversing liver inflammation with beneficial effects on liver injury and hepatic fibrosis.

Geoff Farrell is Professor of Hepatic Medicine at the Australian National University (ANU) in Canberra. He graduated in medicine from the University of Tasmania in 1970, completed an MD by research at the University of Queensland (with Lawrie Powell), and was awarded an NHMRC CJ Martin Fellowship to conduct postdoctoral research with Rudi Schmid at UCSF. In 1980 Geoff returned to establish the Storr Liver Unit at Westmead Hospital, part of the University of Sydney. In 2006, he accepted the position of Professor of Hepatic Medicine, ANU Medical School. His research concerns fatty liver disease especially NASH, ischemia-reperfusion injury, and hepatocellular carcinoma. His published work (4 books, 2 on NASH, more than 200 scientific papers and 150 reviews/chapters/editorials) is highly cited; at least 30 articles have been cited >100 times, 6 more than 500 times, and have influenced thinking in the field as indicated by at least 15 editorials highlighting these contributions. Geoff Farrell has received the Distinguished Research Prize of Gastroenterological Society of Australia, the Eric Susman Prize for Medical Research of the Royal Australasian College of Physicians, delivered the inaugural Zimmerman lecture of the American Association for the Study of Liver Disease in 2002, the 2013 Georges Brohé Medal lecture of the World Congress of Gastroenterology and 8 other named lectureships/orations.

Melanoma heterogeneity

Professor Nickolas Haass

University of Queensland Diamantina Institute/Translational Research Institute

Melanoma drug resistance may be due, in part, to dynamic heterogeneity. Cancer cells within a tumor exhibit various phenotypes in response to environmental stress. This results in populations with different proliferative and invasive capabilities and drug sensitivities. Understanding the molecular signature of dynamic heterogeneity is crucial to design more effective therapies. Using the fluorescence ubiquitination cell cycle indicator (FUCCI) system, which delineates the cell cycle phases by visual means, we found two phenotypic cohorts of xenografts: One contained distinct clusters of either arrested or proliferating cells and another displayed a homogenous dispersion of proliferating cells throughout. The cohorts expressed either low or high levels of microphthalmia-associated transcription factor (MITF), respectively. Silencing MITF by shRNA converted the phenotype. In a 3D spheroid model, MITF was predominantly expressed in the periphery of the spheroid, which corresponded with the region of highly proliferative cells. Forced over-expression of MITF resulted in loss of a distinct proliferative zone, and instead a homogenous growth pattern. Not only do spheroids express MITF around the perimeter, but also markers of the Epithelial to Mesenchymal Transition (EMT), such as Vimentin and Slug, which upon MITF overexpression also switch to become expressed homogeneously. Surprisingly, the increased levels of EMT marker expression by MITF do not correlate to increased migration, and these spheroids in fact show reduced invasion into collagen. Here we show that this is due to altered cell-cell and cell-matrix adhesion. These data outline how dynamic heterogeneity, including proliferative and invasive potential, is tightly intertwined with MITF expression, making it an important marker for therapy design.

Dr. Nikolas Haass is an Associate Professor at the University of Queensland Diamantina Institute/Translational Research Institute. After obtaining his PhD at the German Cancer Research Centre/University of Heidelberg, he trained as a dermatologist at the University Hospital Hamburg-Eppendorf, Germany. He then spent five years as a post-doc at the Wistar Institute/University of Pennsylvania, Philadelphia. In the following five years, he headed the 'Experimental Melanoma Therapy' group at the Centenary Institute/University of Sydney. In March 2013 he commenced his current position at UQDI. Using cutting-edge technology, such as real-time cell cycle imaging, he and his team investigate the biology of tumour heterogeneity with the goal to develop novel therapeutic approaches by simultaneously targeting different melanoma subpopulations.

Control of telomere length: a balancing act

Roger R. Reddel

Children's Medical Research Institute

The chromosomes of human cells terminate in a stretch of repetitive DNA called a telomere, to which specific proteins bind and form a protective nucleoprotein cap. Telomere length is determined by a complex interplay among multiple molecular processes. Every time a cell divides, its telomeres undergo a small amount of shortening, which limits the number of cell divisions. Some normal proliferative tissues require telomere lengthening activity to slow down, but not completely prevent telomere shortening so proliferation can continue throughout the human life span. Telomere shortening contributes to ageing, and hyper-shortening results in short telomere syndromes which have protean clinical manifestations due to premature proliferative failure in various organ systems, such as the bone marrow, lung and liver. In the cells of most, but not all cancers, and in germ-line cells, telomere shortening is completely counteracted by a telomere lengthening mechanism (TLM) – telomerase (a reverse transcriptase) or alternative lengthening of telomeres (ALT; a recombination-dependent process) – which synthesizes new telomeric DNA. If effective TLM inhibitors can be developed, they may potentially be useful for most types of cancers. However, depending on how long they are used for, they may cause side-effects on cells of the germ line and on proliferating tissues. Furthermore, such treatments would not be expected to curb cancer growth until the cancer cell telomeres have become sufficiently shortened to cause growth arrest or cell death, which may take a considerable period of time. Fortunately, up-regulated TLM activity is not the only abnormal feature of telomere biology in cancer cells which could be targeted. Telomeres thus present opportunities for development of therapeutics that modulate age-related diseases and cancer.

Family and genetic studies of major mood disorders

Professor Ian Hickie
University of Sydney

CLINICAL AND APPLIED RESEARCH

Dendritic cell targeting for antigen-specific therapy in early and pre-rheumatoid arthritis

Ranjeny Thomas

University of Queensland Diamantina Institute/Translational Research Institute

Disease modifying strategies are available for treatment of rheumatoid arthritis (RA), and good response rates are achieved. However, limitations include toxicity, a response rate ceiling, cost and rationing of biologic therapies, inability to cure or permanently reverse RA pathology, and inability to prevent disease. Recent evidence suggests that treatment of very early RA with immunomodulatory drugs can delay or attenuate disease onset. RA is strongly associated with the *HLA-DRB1* locus that possesses the “shared susceptibility epitope (SE)”, and the citrullination of self-antigens. Approximately 80% of RA patients develop autoantibodies targeted against citrullinated self peptides. These patients are more likely to have RA-associated HLA-DR risk alleles and to smoke. Using HLA-II tetramers, we demonstrated citrullinated vimentin and aggrecan-specific CD4⁺ T cells in the peripheral blood of *HLA-DRB1*04:01*⁺ RA patients and healthy individuals, and cytokine responses ex vivo. In RA patients, the number of autoreactive cells correlated with disease activity, and the proportion of antigen-specific regulatory T cells was significantly lower than in healthy controls. We are developing antigen-specific immunotherapy to target dendritic cells (DC) in situ with liposomes encapsulating citrullinated peptide and NF-κB inhibitor. In a proof-of-concept trial, delivery of citrullinated peptide and tolerogenic DC was safe and had systemic immune effects. DC represent an important target for citrullinated peptide-specific immunotherapy in RA. HLA-II tetramer biomarkers will be essential to monitor such trials. Antigen-specific therapy has potential for prevention of RA in at-risk individuals with susceptibility genotypes and other risk factors and biomarkers predictive of disease.

The ASPREE (ASpirin in reducing events in the elderly) study of aspirin and healthy ageing

RL Woods¹, JJ McNeil¹, R Grimm² on behalf of the ASPREE investigators³

¹*Department of Epidemiology & Preventive Medicine, ²Monash University, Australia, Berman Center for Clinical Outcomes Research, ³Minneapolis, USA, Multiple Institutions in Australia and the USA*

Understanding factors that contribute to health and disease in our ageing population is a current research agenda, with a key aim to find preventative therapies to keep people healthy for longer. Despite the common use of aspirin for primary prevention of cardiovascular disease in older people, equipoise exists about aspirin's benefits *versus* the risks in the elderly. As we age, there is increasing risk of myocardial infarction, ischaemic stroke, cancer and cognitive decline but also of haemorrhagic stroke and gastro-intestinal bleeding events.

ASPREE is a large-scale (n=19,000) double-blind, placebo-controlled trial of daily low dose (100 mg) aspirin to investigate the overall balance of treatment, particularly whether aspirin can extend disability-free survival over an average of 5 years. The trial is funded primarily by the NIH and is being conducted in persons aged 70+ in Australia and the USA (65+ for US minorities) and who are free of known previous cardiovascular disease, no life threatening illness and with no contraindication to aspirin. The primary endpoint is a composite of death from any cause, dementia or persistent physical disability; an integrated endpoint encompassing the risks and benefits of aspirin. We will also determine the effects of aspirin *versus* placebo on cardiovascular events, cancer, depression and clinically significant bleeding. Community dwelling older adults were recruited through general practices in Australia, with >5000 participants from regional and rural areas, and clinical trial centres in the USA where recruitment is focused on minority groups. The study completed recruitment in December 2014 (16,702 Australian and 2,411 US participants). The main study results are expected by mid- 2018 and will provide information about primary healthcare of the elderly that will change clinical practice in both countries.

A key sub-study of ASPREE, The Healthy Ageing Biobank, collects blood and urine specimens from ASPREE participants on study entry and after 3-4 years on randomised therapy. The Biobank was funded for baseline samples in Australia by the CSIRO and for 3 year follow-up samples in both countries by the National Cancer Institute (NIH). These specimens will enable future studies of biomarkers that may be predictive or diagnostic of older onset disease, or indeed of resistance to illness, due to their linkage with high quality longitudinal data from the clinical trial. For example, biospecimens will be used to answer the questions of whether chronic inflammation underpins cardiovascular disease, dementia, depression or frailty and whether aspirin works by suppressing this inflammation. Other sub-studies (funded by the NHMRC and Monash University) focus on areas relevant to ageing health including age-related macular degeneration, age-related hearing loss, obstructive sleep apnoea, cerebral microhaemorrhages and changes in brain vasculature measured by MRI that may link with declining cognition. A further sub-study is collecting longitudinal data on medical, social, diet and health economic factors that may influence healthy ageing and older onset diseases.

ASPREE is uniquely placed to resolve the equipoise regarding risks *versus* benefits of low dose aspirin for primary prevention in the elderly. In a broader context, the international program of ASPREE and sub-studies will determine factors (clinical, biological, environmental and lifestyle) that may extend disability-free survival. The collaborations between Australia and the USA have enabled this pivotal study of ageing to be conducted across both countries, with funding from the respective key government medical research agencies.

Using individualized randomized trials to improve health outcomes and reduce costs

Mitchell G¹, Nikles J, Senior H, Whitty J, McGree James, Carmont S, Kravitz R, Bazzano L, Schmid C.
¹*Discipline of General Practice, University of Queensland*

Research

Many treatments for chronic disease are amenable to N-of-1 trials, where the physician undertakes a randomized, double-blind, multi-cycle trial to determine whether the treatment is effective for that particular patient against a comparator. The Discipline of General Practice, The University of Queensland (UQ), has clinically validated the use of N-of-1 trials as an effective way to significantly improve health outcomes, promote evidence-based practice and reduce unnecessary medication costs. We are keen to forge new US collaborations and strengthen existing ones, in the area of N-of-1 trials. We aim to improve the health and wellbeing of individuals by ensuring that personalised findings from N-of-1 trials are translated into improved clinical practice and health service delivery.

Current work

- Melatonin in youth with stimulant-treated ADHD. This is an effectiveness trial testing melatonin against placebo in individual patients, and also comparing an RCT design with aggregated N-of-1 trials. We are collaborating with Brown University, US (statistician, Chris Schmid).
- Jane Nikles is on the Scientific Advisory Board for PREEMPT, a US study evaluating smartphone-assisted N-of-1 trials in patients with chronic pain (PI Richard Kravitz, University of California Davis).

Planned work

- We are collaborating with Lydia Bazzano, Ochsner Health System to implement N-of-1 trials on a wider scale in the Ochsner Health System, US. We propose setting up a blueprint for an N-of-1 trial service and using N-of-1 studies to determine the appropriateness of medications for chronic pain as a proof of concept case. This will help to ensure that individuals take the medication that works best for them, thereby reducing adverse events and costs to the health system. We will gather information on the establishment and operation of the N-of-1 trial health service for eventual expansion to other populations and the addition of further medications to be tested.
- We plan to prepare an application to Patient-Centred Outcome Research Institute (PCORI) with Kravitz, Schmid and Bazzano to explore patient needs in N-of-1 trials. We will explore ways to present the results of N-of-1 trials that facilitate patients' understanding, enhance patient autonomy and are useful to doctors.

Impact

We are working with US partners who will act as key site investigators and change agents. This is innovative, pioneering work that will make a difference in the important objective of building a healthier community while reducing the cost of healthcare. It will have far reaching clinical management, policy and economic implications. It could significantly change the face of clinical medicine, in Australia and the US, as well as globally.

Cardiac sympathetic drive mechanisms in heart failure

Clive May

Florey Institute of Neuroscience and Mental Health

Heart failure (HF) is increasingly common due to the improved survival after acute myocardial infarction and the ageing of the population. It is an enormous burden on health budgets costing \$34 billion annually in the US alone. Following a first hospital admission for heart failure, patients have a 5-year mortality of 75%, a survival rate worse than that for most forms of cancer. A hallmark of HF is an increase in sympathetic nerve activity that is initially beneficial, but in the long-term has detrimental effects. In particular, the increase in cardiac sympathetic nerve activity (CSNA) promotes ventricular remodelling and plays a major role in the pathophysiology of arrhythmias and sudden death.

In a series of studies supported by NIH, we have demonstrated that directly recorded CSNA is increased 3 fold in an ovine model of HF, which supports findings of increased cardiac noradrenaline spillover measurements in patients with HF. We have shown that the increase in CSNA is partly dependent on altered reflex control by arterial baroreceptors, cardiopulmonary mechanoreceptors and carotid chemoreceptors. We have demonstrated that the angiotensin type 1 receptor antagonist losartan, given into the brain lateral ventricles of sheep in HF, reduced CSNA to normal, indicating that central angiotensinergic mechanisms play a critical role in driving the increased CSNA. We have investigated which brain sites containing angiotensin receptors mediate this effect of losartan. An important recent finding is that lesion of the area postrema, a brain circumventricular organ, significantly reduced CSNA in ovine HF. Further studies in rats with HF, induced by myocardial infarction, demonstrated that lesion of the area postrema reduced ventricular remodelling and the decline in cardiac function, as measured by ejection fraction and left ventricular end diastolic pressure.

These findings suggest that the area postrema plays a critical role in setting the high level of CSNA in HF, which is detrimental to the outcome of patients with HF. Lesion of the area postrema reduced the ventricular remodelling and decline in cardiac function following myocardial infarction, probably due to the reduction in CSNA. Since the area postrema is outside the blood-brain barrier it is easily accessible circulating drugs and thus may be a novel target for treatment of HF.

Hepatitis C treatment as prevention: challenges and opportunities

Gregory Dore
Kirby Institute, UNSW

Major recent advances in hepatitis C virus (HCV) therapeutic development, with highly curative well tolerated all oral regimens now available have raised the prospect that treatment could provide considerable prevention impact. Mathematical modelling has demonstrated that rapid scale-up of interferon-free direct acting antiviral (DAA) therapy among people who inject drugs (PWID) to levels of 4-8% treated per annum would lead to near elimination of HCV within 20 in settings with a chronic HCV prevalence of 25-50%.

Concerted efforts in several areas are required to enhance the feasibility of HCV treatment as prevention. HCV therapeutic regimens with pangenotypic activity, single daily dosing and short duration (4-6 weeks) would be optimum. HCV screening rates need to be increased, particularly among PWID and HIV-infected men who have sex with men (MSM). HCV treatment infrastructure needs to be broadened to provide access through community-based clinics, drug and alcohol services, harm reduction facilities, and prisons. Community engagement including peer-based worker involvement in HCV screening, disease assessment and treatment delivery programs needs to be developed. Finally, drug price reform and public health advocacy will be instrumental to enable levels of HCV treatment coverage among marginalised populations that would provide major prevention impacts.

Two major Australian HCV treatment as prevention initiatives will be described. The STOP-C project is evaluating HCV treatment as prevention in the prison system in New South Wales. A surveillance phase will monitor HCV incidence in four prisons (two maximum security, two medium security), followed by rapid scale-up of interferon-free DAA therapy with ongoing monitoring of HCV transmission. The CEASE project is evaluating HCV treatment as prevention within the HIV-infected population, predominantly MSM. Components include characterisation of the HIV/HCV population through an observational database (CEASE-d), surveillance for newly acquired HCV and modelling (CEASE-m), education of HIV prescribers in HCV management (CEASE-e) and scale-up of HCV treatment (CEASE-t).

How the Bcl-2 protein family controls cell suicide

Jerry M Adams

The Walter and Eliza Hall Institute of Medical Research

In vertebrates, the commitment of cells to undergo apoptosis, the major form of cell suicide, is determined principally by interactions between opposing factions of the Bcl-2 protein family. A pro-survival faction includes Bcl-2 itself and several close relatives (e.g. Bcl-xL and Mcl-1); they act by sequestering members of the two pro-apoptotic factions: the divergent BH3-only proteins, which in response to intracellular damage convey signals for apoptosis by engaging their globular relatives; and also Bax or Bak, which upon activation convert from inert monomers into lethal oligomers that permeabilize the mitochondrial outer membrane, setting off the proteolytic demolition of the cell.

The first clear link of apoptosis and cancer came in 1988 when our lab showed that the bcl-2 gene, recently discovered by others in a chromosome translocation characteristic of certain leukaemias and lymphomas, promoted cell survival. It is now widely accepted that impaired apoptosis is a hallmark of cancer and a significant barrier to successful therapy. Subsequent work by our lab and many others have clarified how Bcl-2 family members function biochemically and physiologically, in both healthy tissues and in diseased states such as cancer.

Such findings have galvanized the search for small organic molecules that can directly switch on apoptosis in cancer cells to improve cancer therapy. As these potential drugs behave in a fashion like the natural triggers of apoptosis, the BH3-only proteins, they are designated “BH3 mimetics”. The first authentic BH3 mimetic was developed by Abbott Laboratories (now AbbVie). To aid the development of such agents, our institute entered into a research collaboration with Genentech and later AbbVie. The greatest fruit from this very productive tripartite collaboration has been the BH3 mimetic ABT-199, which is highly specific for Bcl-2. It has shown great promise in pre-clinical studies and is now holding that promise in phase 2 and phase 3 studies for chronic lymphocytic leukemia and certain lymphomas. The success of that venture illustrates the power of collaboration between American and Australian science.

Defining tumour specific EGFR antibodies for treatment of advanced cancers.

Andrew M. Scott

Olivia Newton John Cancer Research Institute; La Trobe University; Austin Health

The Epidermal Growth Factor Receptor (EGFR) is expressed in normal tissues and many epithelial cancers, and regulates cellular proliferation and signalling. Overexpression and mutation of EGFR is commonly seen in cancers, and is a target for biologic therapy. Antibodies and small molecule inhibitors of EGFR have shown remarkable success in treating advanced lung, colon and head and neck cancers, and are approved for patient treatment, although toxicity (including rash) is generally dose limiting. In collaboration with scientific colleagues (Ludwig Institute for Cancer Research) in the US, we developed an antibody (mAb806) which binds to a tumour-specific epitope of EGFR, that is only exposed on cancer cells, allowing targeting of tumours without normal tissue toxicity. Our laboratory has demonstrated that mAb806 binds selectively to cancer cells with amplified, overexpressed or mutated (EGFRV8) EGFR, and inhibits signalling and proliferation as well as induces apoptosis in cancer cells. MAb806 causes profound inhibition of tumour growth in animal models, and has enhanced activity when combined with chemotherapy, other EGFR therapeutics, and radiation. We then engineered a humanised form of mAb806, and conducted a first-in-human trial demonstrating selective targeting of EGFR expressing cancers without any toxicity. Our successful initial human trial led to the licencing of mAb806 to a major US Pharmaceutical company (Abbott / AbbVie Pharmaceuticals), and we have worked in partnership with AbbVie to further evaluate mAb806 in Phase I/II human trials. Based on the ability of mAb806 to internalise into EGFR expressing cancer cells, and selective tumour targeting, an antibody-drug conjugate (ADC) form of mAb806 has also been developed (ABT-414) by AbbVie, and we are involved in clinical trials of ABT-414 in glioblastoma multiforme (GBM) patients that are showing remarkable therapeutic responses in Phase I/II trials. Our ongoing laboratory research studies are exploring the optimisation of mAb806 ADCs approaches in a range of tumour types, and defining the structural nature of antibody: EGFR interactions for therapeutic utility.

Development of a monoclonal antibody for prevention and potential treatment of Hendra virus infection

Peter Gray,^a Jeannette Young,^b Geoffrey Playford,^c Michael Gerometta,^a Stephen Mahler,^a Kym Hoyer,^a Martina Jones,^a David Chin,^a Trent Munro,^a Christopher de Bakker,^a Jeff Hou,^a Edwin Huang,^a Matthew Smede,^a Khosrow Aliabadi-Zadeh,^a Emily Chan,^a Kar Man Leung,^a Karen Hughes,^a Ben Hughes,^a Deborah Middleton,^d Linfa Wang,^d Christopher C Broder,^e Zhongyu Zhu^f and Dimitar S Dimitrov^f

^a *Australian Institute for Bioengineering and Nanotechnology, University of Queensland*

^b *Department of Health, Queensland Government*

^c *Department of Health, Queensland Government, Princess Alexandra Hospital*

^d *Australian Animal Health Laboratory, CSIRO Animal, Food and Health Sciences*

^e *Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences*

^f *National Cancer Institute, NIH*

Hendra virus (HeV) is a rare, serious, zoonotic disease with a very high mortality rate. In Australia four of seven human cases have been fatal. The only treatment available for people who are exposed to HeV is a neutralising monoclonal antibody (mAb) m102.4 that binds to the G protein of HeV and Nipah virus (NiV). At present, mAb m102.4 is only available for compassionate use. A large number of organisations have contributed to the development of mAb m102.4 for the prevention and potential treatment of HeV infection. This successful collaboration has included the Commonwealth Government, the NSW and Queensland Governments, the CSIRO Australian Animal Health Laboratory (AAHL), Q-Pharm, the Australian Institute of Bioengineering and Nanotechnology (AIBN) at the University of Queensland, and the Uniformed Services University of the Health Sciences, the Henry M Jackson Foundation for the Advancement of Military Medicine and the National Institutes of Health in the United States. A first-in-man Phase I clinical trial is underway at Q-Pharm in Brisbane, Queensland. Results from the clinical trial are expected by the 1st quarter of 2016. There will be worldwide benefits from this safety trial. NiV is very closely related to HeV and kills hundreds of people each year in Bangladesh and India. Both NiV and HeV could also potentially be used as bioterrorism agents so having an effective, safe treatment to prevent the infection could have huge worldwide benefits.

Targeting Bcl-2-family proteins: a United States-Australia research collaboration.

Wayne J. Fairbrother
Genentech, Inc.

Many cancer cells maintain survival through over-expression of anti-apoptotic Bcl-2 family proteins, making them compelling targets for the development of cancer therapeutics. However, disrupting protein-protein interactions, such as the Bcl-2 or Bcl-x_L interactions with pro-apoptotic BH3 proteins, has been a major challenge for the field. The Bcl-2/Bcl-x_L inhibitor ABT-263 (navitoclax) has shown promising activity in the clinic but its efficacy has been limited by thrombocytopenia caused by Bcl-x_L inhibition. A research collaboration between groups in the USA and Australia led to the design of venetoclax, a Bcl-2-selective inhibitor that maintains efficacy in hematologic malignancies while sparing platelets (Souers *et al.* 2013. *Nature Medicine*). Translational studies that support the use venetoclax in a variety of hematologic malignancies, and results from early clinical studies, will be presented.

Making nanomedicine personal: translating comprehensive genome/transcriptome/epigenome information & point of care diagnostics into the clinic

Matt Trau

University of Queensland, Centre for Personalised NanoMedicine, , Australian Institute for Bioengineering and Nanotechnology (AIBN), School of Chemistry and Molecular Biosciences

Modern medicine is currently transitioning to a new paradigm of precision and personalized care, where patients will be comprehensively screened and monitored for the detailed molecular abnormalities that characterise of their specific disease. In the past decade, nanotechnology has provided new tools (e.g., next-generation sequencing) with unprecedented power to comprehensively interrogate genetic, transcriptomic and epigenetic information. The Centre for Personalised Nanomedicine at UQ is focused on translating these new technologies into a clinical setting, whilst simultaneously developing the next generation of point-of-care diagnostic technologies to further empower the personalised and precision medicine approach. As part of a major National Collaborative grant funded by the National Breast Cancer Foundation (“Enabling clinical epigenetic diagnostics: The next generation of personalized breast cancer care”, CG-12-07), our consortium recently published hundreds of epigenetic regions that area highly informative in cancer¹⁻². These are now being validated in a real-time clinical setting, where comprehensive DNA, meth-DNA and RNA information is collected in tandem and analysed. In this paper we will present data on the clinical translation of this approach, highlighting some of the positive impacts that such an approach can make on the “recovery trajectory” of cancer patients. Along with comprehensive DNA/RNA/methylated-DNA sequencing methodologies, several point-of-care nanotechnologies recently developed by our lab will be presneted³⁻¹². These include novel technologies for detecting circulating free DNA/RNA/meth-DNA, circulated tumour cells, exosomes and protein biomarkers. Several of these technologies have been developed collaboratively with US partners via a M\$5 collaborative NIH grant (“Accelerated Molecular Probe Pipeline”, U01AI082186-01).

Refs:

- 1) Stone, et al., **Nature Communications** (2015)
- 2) Stirzaker, et al., **Nature Communications** (2015)
- 3) Wee, Trau, **Nature Chemistry** (2014)
- 4) Wang, Wee, Trau, **Chem Comm.** (2015)
- 5) Wang, Vaidyanathan, Shiddiky; Trau, **ACS Nano** (2015).
- 6) Vaidyanathan, van Leeuwen, Rauf, Shiddiky, Trau, **Sci Reports** (2015)
- 7) Grewal, Shiddiky, Spadafora, Cangelosi, Trau, **J. Phys. Chem. C** (2015)
- 8) Wee, Sakandar, Shiddiky, Dobrovic, Trau **Clinical Chem.** (2015)
- 9) Korbie, Lin, Wall, Nair, Stirzaker, Clark, Trau, **Clinical Epigenetics** (2015)
- 10) Wee, Lau, Botella, Trau, **Chem Comm** (2015)
- 11) Lane, Korbie, Anderson, Vaidyanathan, Trau, **Sci Reports** (2015)
- 12) Anderson, Lane, Korbie, Trau, **Langmuir** (2015)

Overcoming vaccine design challenges of against old and emerging pathogens

Nikolai Petrovsky

*Director of Endocrinology, Flinders Medical Centre, Medical Professor, Flinders University and
Research Director of Vaxine Pty Ltd*

Modern highly pure vaccines are typically poorly immunogenic, requiring their formulation with an appropriate immune-stimulator (adjuvant) to be effective. Vaxine's Adelaide-based team has been helping address this problem through design of novel adjuvants able to enhance vaccine immunogenicity without compromising vaccine safety and tolerability. Over the last decade Vaxine with ongoing funding support from NIH has partnered with academic and commercial vaccine developers across the US to generate new and improved vaccines against a broad range of biodefense threats including seasonal and pandemic influenza, Japanese encephalitis, West Nile virus, SARS and MERS coronaviruses, HIV, hepatitis B, anthrax, Ebola, RSV, listeria, leishmania, rickettsia, onchocercosis, tuberculosis, polio, malaria, brugia malayi, and even ricin toxin poisoning. Recent data has shown that our technologies can even enhance vaccine protection in pregnant mothers, neonates and the elderly, all traditionally poor vaccine responder populations. These vaccine development programs have required use of an extraordinary diversity of specialised animal challenge models including mice, rats, guinea pigs, rabbits, gerbils, ferrets, sheep, chickens, goats, llamas, horses and camels, in addition to access to specialised facilities including the Australian synchrotron and NCMAS supercomputer facility, Stanford University CyTOF and BSL3 and BSL4 animal challenge facilities managed by NIH and USAMRIID. This Australian-US vaccine partnership has already yielded more than 40 scientific publications, multiple patents, numerous vaccines in various stages of preclinical development and human clinical trials of vaccines against pandemic and seasonal influenza, hepatitis B and allergy. In partnership with USAMRIID exciting new data has been generated applying our adjuvant technology to their Ebola vaccine, and with NIH and Colorado State University we have been contributing to a novel MERS vaccine for camels. We have been working with Bill and Melinda Gates Foundation on a next generation inactivated polio vaccine and recent exciting project has been to apply our adjuvant technology to an Alzheimer's disease vaccine developed by UCI-Mind in California, with promising results recently attracting a NIH U01 grant to enable advance clinical development of this Alzheimer's vaccine. Alongside our advanced clinical development programs, the Vaxine team is also heavily engaged in basic science to unravel the cellular mechanisms of action of vaccine adjuvants, and with support from a recent HHS/NIH 5 year contract we are applying high-throughput screening methods including advanced high performance computer modelling approaches to discover new adjuvant candidates. Most excitingly we have started to decipher in human subjects how our adjuvant technologies are able to broaden B-cell responses within virus families, thereby providing the opportunity to produce vaccines that provide more cross-protection. Notably, without the long-term support of NIH and our many US-based collaborators few of these achievements would have been possible.

PUBLIC AND MENTAL HEALTH

Targeting the urgent global medical challenge due to antibiotic resistance: A US-Australian collaborative program

Professor Jian Li, PhD
Monash Institute of Pharmaceutical Sciences, Monash University

The lack of new antibiotics presents an unmet global medical need. The Infectious Diseases Society of America (IDSA) and the Centers for Disease Control and Prevention (CDC) have identified several bacterial 'superbugs' which are resistant to almost all current antibiotics. Novel antibiotics are urgently required - in particular, no novel antibiotics will be available for many years to come against the Gram-negative 'superbugs', namely *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Polymyxins (i.e. colistin and polymyxin B) are increasingly used as the last-line option for treatment of infections caused by these three problematic Gram-negative 'superbugs'. Initiated in Australia in 1999, our polymyxin research program has provided the majority of modern pharmacological data, demonstrating that currently recommended dosage regimens of polymyxins are sub-optimal and nephrotoxicity is a major dosing-limiting factor. Disturbingly, the emergence of polymyxin resistance has been reported in many countries, possibly due to sub-optimal use. Resistance to polymyxins means virtually no antibiotic will be available for clinicians to use for treatment of life-threatening infections caused by the aforementioned Gram-negative 'superbugs'. Our NIH-funded multi-disciplinary research program includes: (1) optimizing the clinical use of colistin and polymyxin B in different types of critically-ill patients; (2) elucidating the mechanisms of their antibacterial activity, resistance and nephrotoxicity using a systems pharmacology approach; (3) developing rational polymyxin combinations and novel dosing regimens of polymyxins with other antibiotics, in particular carbapenems; (4) identifying innovative polymyxin combinations with FDA-approved non-antibiotic drugs using systems biology; and (5) discovering novel, safer polymyxins based on the mechanistic and pharmacological knowledge base we have acquired in the past 16 years. Our US collaborators at Rempex Pharmaceuticals (CA), the University at Buffalo (NY), and Wayne State University (MI) / University of Pittsburgh (NJ) provide drug development expertise, pharmacometrics skills and clinical support, respectively, to our polymyxin research and discovery program. Two of my five R01 grants were highlighted by the US President Barack Obama at the meeting with the Australian Prime Minister Tony Abbott on 12 June 2014, as one of the 6 examples of U.S.-Australia innovation and science cooperation. In the battle against rapidly emerging Gram-negative bacterial resistance, it is imperative to pursue rational approaches to the use of existing drugs and discover a new-generation of safer antibiotics. Our collaborative polymyxin program highlights the significance of US-Australian collaborations in targeting the urgent global medical challenge due to antibiotic resistance.

Acknowledgment: NIH funding:

R01AI098771, R01AI111990, R01AI111965, R01AI079330 and R01AI070896

Supporting new vaccine introduction in the Asia-Pacific region: highlighting the importance of U.S.-Australia research collaboration

A/Prof Fiona Russell
*Centre for International Child Health,
WHO Collaborating Centre for Research and Training in Child and Neonatal Health,
Dept. of Paediatrics, The University of Melbourne
Pneumococcal Research Group,
Murdoch Childrens Research Institute, The Royal Children's Hospital,*

Diseases caused by *Streptococcus pneumoniae* (the pneumococcus) constitute a major global health problem. It was estimated that in the year 2000, about 14.5 million episodes of serious pneumococcal disease occurred, resulting in about 826,000 deaths in young children. Serious diseases that are often caused by pneumococci include pneumonia, meningitis and sepsis.

In 2001, a meeting was held at the National Institutes of Health (NIH), USA, to determine global research priorities to facilitate the use of pneumococcal vaccines in resource-limited countries. Our vaccine trial was formulated to address a global research priority for resource-limited countries: the evaluation of a more appropriate and affordable pneumococcal immunisation schedule. We combined fewer doses of the 7-valent PCV (PCV7) in infancy with a subsequent “booster” dose of the 23-valent polysaccharide vaccine (23vPPS).

This vaccine trial was administered by The University of Melbourne, in collaboration with the Fiji Ministry of Health from 2003 to 2009. It was jointly funded by the DMID, NIH, USA (US\$2.62m), and NHMRC (\$1.59m). Funds from NIH were used for the fieldwork in Fiji. Funds from NHMRC were used to establish state-of-the-art immunology and microbiology laboratories.

We disseminated our results to immunisation policy makers in Fiji, Australia, and WHO. Our results were presented at international conferences and to funding bodies including NIH, Australian Aid, and the Gavi Alliance. Our results contributed to changes in the Fijian, Australian, and WHO PCV immunisation policy. This included the discontinuation of 23vPPS for young children primed with PCV7, and the revision of the WHO PCV Position Paper which now includes a “2+1” schedule. Fiji introduced PCV into their national program with Australian Aid support and we are currently leading an Australian Aid-funded project to evaluate the impact of PCV in Fiji. The pneumococcal laboratory at MCRI is now a recognised leader in the evaluation of pneumococcal vaccines. The success of the project has led to other high profile projects including an NIH-funded Fiji follow-up study and a number of Bill & Melinda Gates Foundation and Gavi Alliance funded projects, and other new vaccine work in the Asia-Pacific region.

Chalky teeth: a global health problem that bypassed the USA?

Professor Mike Hubbard
University of Melbourne

Chalky teeth are a silent but major public health problem, affecting about 1-in-6 schoolchildren worldwide and triggering >50% of childhood tooth decay. Being causally linked to infantile illness, it seems this medico-dental problem might become preventable medically once the causes are found. Curiously, in the USA, the chalky teeth problem is almost totally unrecognised by dentists, doctors, researchers and the public health system. How can this be, and what can be done about it?

Building on a strong research heritage, Australasian stakeholders have established a world-first translational research and education network seeking better understanding and care of people with chalky teeth (www.thed3group.org). A variety of educational resources have been developed through cross-sector collaboration (academia, practitioners, affected families, industry), with strategic focus on educating the public about research needs. And breakthrough translational research has led to surprising insights about cause, plus development of a new diagnostic.

Large opportunity exists for useful USA-Australia partnership on this problem. The cross-sector translational network seems like a sensible approach for tackling the numerous challenges involved.

Non-hormonal male contraception via pharmacological blockade of sperm transport

Sabatino Ventura

Monash Institute of Pharmaceutical Sciences, Monash University.

According to the World Health Organization, there are 75 million unwanted pregnancies worldwide each year. Aside from the issue of global overpopulation, this is also a problem in both the U.S.A. and Australia. The NIH reported that in 2002, 49% or 2.65 million pregnancies (including abortions) in the U.S.A. were reported as unintended. Similarly, the Australian Bureau of Statistics recorded a teenage birthrate of ~15 per 1000 women in Australia in 2012, higher than most other developed countries. While present contraceptive methods are effective, there is clearly a need to develop additional methods of contraception for males, a market which is clearly lacking. Therapeutic targets for male contraception are associated with numerous problems due to their focus on disrupting spermatogenesis or hormonal mechanisms to produce dysfunctional sperm. This project describes the dual genetic deletion of α_{1A} -adrenoceptors and P2X1-purinoceptors in male mice thereby blocking sympathetically mediated sperm transport through the vas deferens during the emission phase of ejaculation. This modification produced 100% infertility without effects on sexual behaviour or function. Sperm taken from the cauda epididymides of double knockout mice were microscopically normal and motile. Furthermore, double knockout sperm were capable of producing normal offspring following intracytoplasmic sperm injection into wild type ova and implantation of the fertilized eggs into foster mothers. Blood pressure and baroreflex function was reduced in double knockout mice but no more than single knockout of α_{1A} -adrenoceptors alone. These results suggest that this autonomic method of male contraception appears free from major physiological and behavioural side effects. In addition, they provide conclusive proof of concept that pharmacological antagonism of the P2X1-purinoceptor and α_{1A} -adrenoceptor provides a safe and effective therapeutic target for a non-hormonal, readily reversible male contraceptive.

Point-of-care nucleic acid detection to control sexually transmitted infections and their adverse health outcomes in low income and remote settings.

John Kaldor
Kirby Institute, University of New South Wales

The nucleic acid detection methods that have revolutionised the diagnosis, management and investigation of infectious disease have until recently been infeasible for low income countries. Even in high income countries they have required the use of expensive equipment based in sophisticated, centrally located laboratories, and have therefore not been amenable to use in smaller health facilities. The development by Cepheid of the GeneXpert, a highly accurate point-of-care system for nucleic acid detection that can be used in field settings with relatively limited training, has redefined tuberculosis control strategies and is promising to offer new opportunities across a number of other disease areas. We have initiated field investigations of the role of this technology in remote and resource limited settings for the diagnosis and management of sexually transmitted infections. Gonorrhoea, chlamydia and trichomoniasis are readily curable microbial infections that occur at high levels. While easily treatable if detected, their diagnosis in low income settings has been largely based on syndromic algorithms that are notoriously inaccurate, particular for infections in women, so there can be little confidence that infections are being detected and treated in a timely manner. In 2013, we began a trial in a number of remote Aboriginal communities in central and northern Australia, where these infections are also prevalent, and people offered testing must often wait weeks for a diagnosis based on a specimen sent to a major centre. Findings from the trial so far have shown that the point-of-care technology is well accepted by clinicians (doctors, nurses and Aboriginal health providers), is equal in accuracy to the conventional laboratory based tests, and results in a massive reduction in time to treatment. The ultimate goal of the trial is to determine whether the use of the technology increases the number of people correctly treated and reduces re-infection rates. In 2014, a field trial began of the use of the tests in the district hospital setting in Papua New Guinea, and again high levels of accuracy and clinician acceptability were confirmed. Plans are now underway for a large-scale trial of screening and treatment for the three infections in pregnancy, to determine whether this intervention reduces levels of prematurity and low birth weight. Another area of potential application of the point of care technology is in the control of cervical cancer, the most important malignant disease in women in many developing countries where there has been very limited access to early detection and effective treatment. Although a highly effective vaccine against the causative agent for cervical cancer, human papillomavirus, is now available it is yet to make inroads into most low income settings and in any case will be of no benefit to the many women who have already acquired infection with the virus. A new project, also being undertaken in Papua New Guinea, aims to investigate the use of the point-of-care technology to detect infection with high-risk types of the virus, and therefore serve as a triage mechanism for deciding which women should be offered further investigation and ultimately treatment for cervical cancer and pre-cancer. Initial findings have confirmed the accuracy of the point-of-care test for high risk types of human papillomavirus under field conditions and are now leading to a more detailed assessment of its predictive value for disease. Although point-of-care technology for nucleic acid detection is currently out of reach for routine use in low income countries, evaluations of the kind described here will provide the evidence based needed for making decisions as to whether it is an effective intervention that should be developed for this setting. STIs are common in many low income countries, and are important causes of adverse reproductive outcomes.

Clinical studies in stroke: US and Australian links

Geoffrey A Donnan

The Florey Institute of Neuroscience and Mental Health

Stroke is the second most common cause of death globally and major cause of disability hence new interventions are likely to have significant public health implications. In acute stroke there have been remarkable advances in means of reducing mortality and improving clinical outcomes over the last 20 years. Because of commonalities of clinical research approaches there are frequent examples of collaborative initiatives between Australia and the USA. From the Australian end, coordination of neuroscience clinical trials within the framework of the clinical research organisation Neuroscience Trials Australian (NTA) greatly facilitates global collaboration. For example NTA has helped coordinate a number of recent NIH funded trials, two of which are ongoing and one has been completed. The Interventional Management Study 3 (IMS3) was designed to test the hypotheses that clot extraction from intra cerebral vessels using a stent retriever device would improve clinical outcomes. While the trial did not support the hypotheses, it was an important prelude to other studies including the Australian EXTEND-IA trial which showed significant benefit for this procedure. With a number needed to treat of only three, this form of intervention is likely to have profound effects on the way stroke services are organised around the world and eventually have a significant impact on case fatality rates.

In summary, there are significant collaborative studies being undertaken between the US and Australia in the field of stroke. There are real opportunities to expand this arrangement given the excellent collaborative spirit which exists and consideration for some innovative new ways of funding.

A novel endovascular neural recording device

Sam John

Department of Electrical and Electronic Engineering, Melbourne School of Engineering, University of Melbourne

High-fidelity cortical arrays for recording and stimulating brain activity have lead to major advances in the diagnosis, management and treatment of several neurological conditions over the last decade. Traditional arrays require direct implantation into the brain via open craniotomy, which can lead to inflammatory tissue responses and may disrupt or reduce the ability to detect chronic neural activity. There is a need to develop minimally invasive approaches that avoid brain trauma. Inspired by the long-term stability of devices implanted into blood vessels, including the artificial cardiac pacemaker, we have demonstrated the feasibility of chronically recording brain activity from within a vein. We developed a stent-electrode array (stentrode), capable of being implanted into a superficial cortical vein overlying motor cortex via catheter angiography. The stentrode may have wide ranging clinical applications for long-term treatment of neurological conditions and brain-machine interfaces.

Genetic screening for prevention of severe cutaneous reactions to antiepileptic drugs: from discovery to practice

Professor Patrick Kwan
University of Melbourne

Pharmacogenetics is a burgeoning field in clinical practice and forms the backbone of precision medicine. However, little is known about the health economics impact of pharmacogenetic screening in real-world practice. Carbamazepine is a first-line antiepileptic drug for people with epilepsy. In the initial stage of treatment, carbamazepine may induce serious idiosyncratic cutaneous reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Carbamazepine-induced SJS/TEN is strongly associated with HLA-B*15:02 among people of Asian ancestry, of whom up to 15% carry the allele. Pharmacogenetic screening of HLA-B*15:02 prior to commencing carbamazepine is recommended by major regulatory agencies in the world, and has been implemented at system-wide level in certain countries. In the research setting, HLA-B*15:02 screening significantly reduced the incidence of carbamazepine-induced SJS/TEN among Han Chinese, and economic modeling suggested that screening would be cost-effective in high risk populations.

While these studies have provided evidence of the potential health and economic benefits of a HLA-B*15:02 screening policy, they do not take into account possible effects such a policy may have on actual clinical practice. Using real world data from Hong Kong, we showed that the HLA-B*15:02 screening policy has had significant impact on antiepileptic drug prescriptions, and the overall incidence of antiepileptic drug-induced SJS has not be reduced. As a result, the screening policy, as it is currently practiced, is not cost-effectiveness. We proposed that the cost-effectiveness of the screening can be improved by rapid point-of-care testing.

The neural bases of decision-making

Bernard Balleine

Brain & Mind Research Institute, University of Sydney.

The smooth integration of cognitive and emotional processes is necessary for everyday decisions. Dysfunction in this integrative capacity accompanies many major psychiatric conditions, neurodegenerative disorders and drug addiction. Changes in the neural systems that result in the cognitive and emotional dissociation reflected in these disorders constitute the highest health, economic and social capital attrition burden of any disease group, a burden that is only predicted to increase as the population ages. Understanding these changes in neural systems and their specific behavioural effects is, therefore, of critical importance and will ultimately provide new targets for treatment and rehabilitation. We seek, therefore, to understand the neural bases of cognitive and emotional integration in decision-making using state of the art computational, behavioural, cellular, molecular and imaging tools to map the functional systems and circuits controlling action planning, selection, evaluation and choice. Aspects of this program of research involve collaboration with scientists at Caltech (imaging the cortical-basal ganglia network in the cognitive control of action) and at UCLA (investigating the amygdala-striatal network in emotional processes that support reward learning). This research has been funded by RO1's from various of the National Institutes of Health, including the NIMH, NICHD and the NIAAA, a center grant from the NIDA, and by research grants from the NHMRC and ARC in Australia, including an ARC Laurent Fellowship.

Recent advances in molecular point of care devices for neurological and psychiatric applications

E. Skafidas
University of Melbourne

Medical practitioners require timely access to high quality patient data for the best management and treatment of their patients.

A standard pathology test today is complex, time consuming, expensive to the health system and in many cases inconvenient for the patient. As an example, an outpatient blood based pathology test begins at practitioner's office where upon deciding upon a set of tests, writes an order for the required tests. This order is then handed to the patient. The patient travels to the local pathology service where the phlebotomist draws the sample of blood. This sample is sent to the laboratory for processing. Upon processing, the test results are forwarded to the practitioner for interpretation. The patient needs to re visit the medical practitioner to obtain the results, receive treatment. If the results are inconclusive new tests will need to be ordered.

Molecular point of care devices promise to deliver new ways for medical practitioners to obtain the relevant information in a more convenient and timely manner.

This paper will outline technology advances in point of care devices that are now permitting low cost and easy to use in clinic and bedside diagnostics.

The paper will outline these technology advances with three specific example applications and our preliminary results for each, namely:

1. Point of care system for bacterial identification and antibiotic sensitivity determination. (Immuno compromised, Immuno Supressed Patients)
2. Rapid point of care ELISA synthesis. The engineering of new detection sensors and new techniques for rapid synthesis of plastic antibodies will be outlined
3. Point of Care pharmaceutical level testing. Anti psychotic (Clozapine)

BIOGRAPHIES AND SCIENTIFIC INTERESTS

Professor Ian Frazer, M.D., FRCPA, FRCP (Ed), MB ChB, B.Sc.

Director, Translational Research Institute, University of Queensland



Dr Ian Frazer is a clinician scientist, trained as a clinical immunologist in Scotland. As a professor at the University of Queensland, he leads a research group working at TRI in Brisbane, Australia on the immunobiology of epithelial cancers. He is recognised as co-inventor of the technology enabling the HPV vaccines, currently used worldwide to help prevent cervical cancer. He heads a biotechnology company, Admedus Vaccines, working on new vaccine technologies, and is a board member of several companies and not for profit organisations. He is current president of the Australian Academy of Health and Medical Sciences, and a member of the Commonwealth Science Council.

Prof Frazer has a longstanding collaboration with Prof Paul Lambert at the McArdle institute in Madison, Wisconsin, researching the immunological consequences of papillomavirus infection and associated cancers

He was recognised as Australian of the Year in 2006. He was recipient of the Prime Ministers Prize for Science, and of the Balzan Prize, in 2008, and was elected Fellow of the Royal Society of London in 2012.

He was appointed Companion of the Order of Australia in the Queen's Birthday Honours list in 2013.

Professor Simon Foote

Director, John Curtin School of Medical Research



Professor Foote received his MBBS and PhD from the University of Melbourne and his DSc from the University of Tasmania. He did his postdoctoral training at the Whitehead Institute at MIT, Massachusetts and has worked as Division Head at the Walter and Eliza Hall Institute, Melbourne and Director at the Menzies Research Institute Tasmania. From 2012-2014 he was Dean of the Australian School of Medicine at Macquarie University and has been Director of ANU's John Curtin School of Medical Research since 2014.

Foote is interested in the genetic control of susceptibility to disease, with particular focus on infectious disease. His laboratory has identified loci governing the response to leishmaniasis and malaria. However the major focus of the laboratory is on trying to identify new drugs to combat malaria. By using the example of natural mutations that affect the red cell and making it difficult for the parasite to grow, his laboratory has found genes, that when mutated, prevent growth of malarial parasites. These genetic changes point the way to the creation of a new type of treatment that will be steadfast against the development of drug resistance. His laboratory is also interested in the genetic susceptibility to other diseases of humans. He is currently working on investigating the reasons that renal disease is so common in Aboriginal communities and in the genetic changes that underpin the familial nature of some of the common cancers.

PROFESSOR SHARON LEWIN

*Director, The Doherty Institute
Professor, University of Melbourne
Co-Head for Virology, The Burnet Institute
Director, Alfred Health*



Sharon Lewin is an infectious diseases physician and basic scientist. She is Director of The Doherty Institute. Sharon is also Director of the Infectious Diseases Unit at The Alfred; Professor of Medicine, Department of Medicine, Monash University in Melbourne and an NHMRC Practitioner Fellow.

Sharon completed her medical training at Monash University, followed by a PhD in virology at the Burnet Institute in Melbourne and a post-doctoral fellowship at the Aaron Diamond AIDS Research Center, The Rockefeller University in New York.

She is the immediate past president of the Australasian Society for HIV Medicine and is currently a member of the Ministerial Advisory Board on Blood Borne Viruses and Sexually Transmitted Infections (STIs), the peak advisory body to the Health Minister on matters related to HIV, viral hepatitis and STIs. She was the co-chair of the International AIDS Conference, the major international conference for HIV, which was held in Melbourne 2014.

Professor Lewin's research focus is in translational and clinical studies of HIV infection. She heads a research team of over 25 scientists and clinicians who are trying to understand why HIV persists on antiretroviral therapy (ART) and finding a cure for HIV to allow people living with HIV to safely stop ART without the virus returning. Her major contributions have been the development of very sensitive tools to quantify virus in HIV-infected individuals on antiretroviral therapy, the development of in vitro models to understand how HIV latency is established, maintained and reversed and to test interventions that reverse HIV latency in the context of clinical trials. The current main themes of her research are related to the role of histone deacetylase inhibitors, chemokines and dendritic cells in HIV latency. Her other main interests have been in understanding how the immune system recovers following ART and the origin and function of new T-cells and the role of inflammation in non AIDS diseases including cardiovascular and liver disease. This work is now largely performed in collaboration with investigators in Malaysia. She has had a long standing interest in co-infections that occur at a high frequency in people living with HIV in low income countries. Her major focus has been in HIV-hepatitis B virus (HBV) co-infection and understanding the drivers of liver disease in this setting and antiviral drug resistance. This work is largely done with collaborators in Bangkok. Recently she has led studies understanding the impact of a recovering immune system on cryptococcal infection which occurs at high frequency in HIV-infected patients living in Africa

She was named Melbourne of the Year in 2014

Professor Jonathan Cebon

Medical Director of the Olivia Newton-John Cancer (ONJ) Research Institute and Medical Director of Cancer Services at Austin Health in Heidelberg VIC



Professor Cebon is a clinician researcher, Medical Director of the Olivia Newton-John Cancer (ONJ) Research Institute and Medical Director of Cancer Services at Austin Health in Heidelberg VIC. He is a Professor in Medicine at the University of Melbourne and Fellow of the Royal Australasian College of Physicians. He serves on the Cancer Council of Victoria and is a member of the Consultative Council of the Victorian Cancer Agency and is a member of Cancer Trials Australia.

The focus of his clinical practice and research program over 20 years has been melanoma and the immune therapy of cancer. He has received career-long research support from the Ludwig Institute for Cancer Research and grant support from Melanoma Research Alliance, Cancer Vaccine Collaborative (CVC) and Cancer Research Institute (CRI); all of which are US-based organizations that play a major international role supporting basic, translational & clinical research into the immune therapy of cancer. Additionally the ONJ Cancer Centre is a leading Australian clinical trials site for the development of cancer therapeutics and runs more than 70 clinical trials at any one time, many of which are sponsored by US pharma.

Professor Jillian Kril

Professor of Neuropathology and Associate Dean (Research), University of Sydney



Jillian Kril is Professor of Neuropathology and Associate Dean (Research) for the Sydney Medical School at The University of Sydney. In addition, she is Director of the NSW Brain Tissue Resource Centre (NSW BTRC) and Deputy Director of the Australian Brain Bank Network. Jillian has over 20y experience in human neuropathology in the areas of research, teaching & clinical service.

Jillian has a long-standing interest in the neuropathology of alcohol-related brain damage and neurodegenerative diseases. Her research examines the extent and topography of neuronal loss and degeneration in ageing, alcoholism and dementia. She developed techniques for the volumetric analysis of postmortem brains and studies the correlation between brain pathology, including abnormal proteinopathies, and the clinical symptoms and signs present in neurological diseases. To achieve this she applies a wide range of methodologies including anatomical, histological, immunohistochemical, receptor binding, ELISA, transcriptomic, genetic and biochemical techniques. Jillian's research career has yielded over 175 peer-reviewed publications with 22 that have been cited >100 times. She has also authored the sections on alcohol-related brain damage, vitamin deficiencies and hepatic encephalopathy for the 8th and 9th editions of the premier neuropathology textbook *Greenfield's Neuropathology*.

The NSW BTRC, which is funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA), is responsible for the collection, characterisation and distribution of brain tissue to researchers worldwide. Operational since 2000 this resource has facilitated over 100 research projects and resulted in more than 300 publications. The associated brain donor program also follows >550 consented donors, collecting demographic, medical and lifestyle information. The NSW BTRC has collaborations with a number of researchers including Drs Harris and Mayfield at the University of Texas at Austin and Dr Suzanne de la Monte at Brown University.

Professor Matt Trau

Deputy director and a co-founder of the Australian Institute for Bioengineering and Nanotechnology (AIBN).



Matt Trau is currently a Professor of Chemistry at the University of Queensland (UQ) and is also deputy director and a co-founder of the Australian Institute for Bioengineering and Nanotechnology (AIBN). Since graduating from the University of Sydney (BSc Hons I, University Medal) and the University of Melbourne (PhD in Physical Chemistry, 1993), he has held positions within industry and academia across the globe. These include a Fulbright Research Fellowship at Princeton University, USA, a research scientist at Dow Chemical and ICI Pty Ltd. Matt has also been a Visiting Professor at two of the largest Cancer Research Centres in the world: The Dana Farber Cancer Research Institute, Harvard Medical School, Boston (2000), and the Fred Hutchinson Cancer Research Centre, Seattle (2008). Matt is internationally recognised for his innovative and cross-disciplinary research at the interface between chemistry, nanotechnology, biology and medicine. He has co-authored more than 130 publications, many of which appear in the highest impact journals in his field, e.g., 4 highly cited publications in *Nature* and *Science* on independent nanotechnology innovations (eight *Science* and *Nature* family journal publications overall to date). His major awards and honours include an Australian Research Council Federation Fellowship (one of the most prestigious scientific fellowships in Australia), a Fulbright Research Fellowship to the US, a "Young Tall Poppy" Award for Queensland, a UQ Foundation/Vice Chancellor's Research Excellence Award, a Paul Harris Fellowship, and a Pink Circle Award for breast cancer research excellence.

Matt has raised more than \$24 million in competitive national and international grant funding in the past 10 years. In the last five years, Matt has initiated and led several large international programs that involve close collaboration between leading nanotechnologists, molecular biologists, geneticists and commercial researchers - with the goal of creating cutting edge diagnostics. These include a \$4 million National and International Research Alliances Program (NIRAP) grant from the Queensland government ("International Partnership for preventative and Personalised Medicine"); and two consecutive \$5 million multidisciplinary collaborative grants from the National Breast Cancer Foundation (NBCF): "Novel strategies for Prediction and Control of Advanced Breast Cancer via Nanoscaled Epigenetic-Based Biosensors", 2008-2013; and "Enabling Clinical Epigenetic Diagnostics: The Next Generation of Personalized Breast Cancer Care", 2013-2018. These grants involve research collaborations with some of the highest calibre scientists in the world, e.g., Dr Lee Hartwell (2001 Nobel Laureate) from Seattle was a co-chief investigator on the NIRAP grant, and each of the NBCF grants include leading geneticists, pathologists and oncologists from across Australia and around the world. Matt was also a co-PI on a M\$5 NIH grant with Prof Jerry Cangelosi from the University of Washington ("Accelerated Molecular Probe pipeline", U01AI082186-01). His lab is also growing collaborations with Dr Leroy Hood at the Institute for Systems Biology in Seattle.

Professor Jerry Adams

Joint Head of the Molecular Genetics of Cancer Division of the Walter and Eliza Hall Institute of Medical Research



Professor Jerry Adams is currently Joint Head of the Molecular Genetics of Cancer Division of the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia; Director of a Specialized Center of Research established there by the US-based Leukemia and Lymphoma Society, and Professor of Molecular Genetics of the University of Melbourne.

Professor Jerry Adams was born in Columbus, Georgia, USA in 1940. After undergraduate studies at Emory University in Atlanta, Georgia, he did PhD studies at Harvard University with James D Watson (1962-1966) and post-doctoral studies with Frederick Sanger (1967-1968) at the Laboratory of Molecular Biology in Cambridge, where he met Suzanne Cory, who became his career-long collaborator.

After further molecular biology studies in Geneva, Switzerland, in 1972 they took positions in the Walter and Eliza Hall Institute and initially investigated the genetic basis of antibody diversity. Since 1982, Professor Jerry Adams and colleagues have focussed on the genetic basis of cancer. His most notable discoveries have concerned the role of chromosome translocations and cell death in cancer development.

Following their seminal discovery that cell death (apoptosis) is impaired in cancer cells, they have concentrated on the roles of apoptosis in cancer, the mechanisms that control cell death and potential ways of exploiting the apoptotic machinery to improve therapy.

Professor Jerry Adams research has led to over 200 scientific publications, collectively cited over 18,000 times, and has been recognized by a number of awards, most notably by his election to the Australian Academy of Science (1986) and the Royal Society (1992).

Professor Jian Li

Monash University



Professor Jian Li represents one of medical science's last defences against the ongoing march of the bacterial 'superbugs'. He is a world leader in the pharmacology of polymyxin, one of the few antibiotics currently available that is still capable of successfully fighting bacteria which have become resistant to just about every other antibiotic on the market.

Jian started his research in colistin pharmacology while working as a PhD student.

Jian and his PhD supervisors realised that it could offer a new hope for treatment of infections caused by Gram-negative superbugs. Since then, Jian, and his team have led a relentless exploration of pharmacology of colistin and polymyxin B. Today they provide the majority of our current knowledge on this class of antibiotics.

Over the last 8 years he and his collaborators have attracted more than \$15 million in competitive grant funding from Australian government (i.e. National Health and Medical Research Council), the National Institutes of Health (USA) and the pharmaceutical industry.

His work has exposed polymyxins to the rigours of modern drug development procedure that was not in place when this old class of antibiotics was first introduced to hospitals.

His group has taken the drug from the earliest stages of microbiological evaluations and animal testing through to clinical studies. More than 250 patients across the USA, Thailand, Greece and Brazil participated in clinical studies. The samples being sent to Monash for pharmacological analyses have generated optimism that colistin could be used in the fight against superbugs. In addition, Jian is leading a very productive team at Monash to discover novel lipopeptides which are active against polymyxin-resistant superbugs.

"The current antibiotic discovery pipeline is dry; there's no new antibiotic for these sorts of pathogens for many years to come," Jian says. "It's an urgent situation, globally. As highlighted on World Health Day 2011: no action today, no cure tomorrow. We hope our discovery could be part of the solution."

Jian has established a team of cross-disciplinary experts within the Monash Institute of Pharmaceutical Sciences and Monash University to uncover the basic mechanisms of bacterial resistance and toxicity to further enhance his drug discovery program. This world-leading research will help slow the advance of bacterial resistance and minimise side-effects in patients.

"The rise of bacterial superbugs is inevitable, and has presented a global medical challenge, including in Australia. At the moment polymyxins are considered a last line therapy; they are one of the best weapons left in the fight against superbugs."

Professor Geoffrey A Donnan

Director, The Florey Institute of Neuroscience and Mental Health, Melbourne



Professor Geoffrey Donnan's research interest is clinical stroke management. He was co-founder with Stephen Davis of the Australian Stroke Trials Network (ASTN) within which there have been conducted numerous investigator driven and other stroke trials. The first of these was the Australian Streptokinase Trial (ASK), which he led with Stephen Davis. He has since been involved in numerous clinical trials of therapy as Chair, Co-chair or Steering Committee member. These include ECASS II and more recently EPITHET. He is currently Co-chair of the EXTEND group of trials, including the EXTEND IA trial of thrombectomy in acute ischaemic stroke published in the NEJM, again with Stephen Davis. With Julie Bernhardt and Helen Dewey, he recently completed the global trial of early rehabilitation published in Lancet. He co-founded the Australian Stroke Trials Network and more recently Neurosciences Trials Australia. He also has a major interest in the imaging of the ischaemic penumbra and the interface between basic sciences and clinical stroke medicine, and in collaboration with Malcolm Macleod and David Howells, he has adapted the meta-analysis technique to assess therapies in animal stroke models.

He has close collaborations with colleagues conducting clinical trials in the US, particularly Greg Albers at Stanford University Department of Neurology with meta analyses of mutual EPITHET and DEFFUSE stroke trials. These trials are designed to extend the time window for intravenous thrombolytic therapy using sophisticated imaging selection techniques. Professor Donnan has also served on NIH committees to prioritise stroke research over the next decade, many of the findings from which are currently being implemented.